Amendments to the Specification

Please replace paragraphs in the specification with the corresponding replacement paragraphs, below.

[0036] Figures 5A and 5B, taken together, are a flow diagram which represents the ~~StellaTM~~ STELLA® computer model simulation of the pharmacokinetics of the administration of a single opioid. Figure 5A shows the Device Model and Pharmacokinetic Model aspects of the simulation, Figure 5B shows the Ventilatory Depression Model and the Sedation Model aspects of the simulation.

[0038] Figure 7 is a graph showing the time course of ventilatory depression in the ~~StellaTM~~ STELLA® computer model simulation of Figures 5A and 5B (ventilatory depression and sedation models disabled).

[0040] Figure 9 is a graph showing the time course of ventilatory depression in the ~~StellaTM~~ STELLA® computer model simulation of Figures 5A and 5B (ventilatory depression model enabled, sedation model disabled).

[0041] Figure 10 is a graph showing the time course of quantity of opioid in the inhalation device and in the lung of the patient, in the ~~StellaTM~~ STELLA® computer model simulation of Figures 5A and 5B (ventilatory depression and sedation models enabled).

[0042] Figure 11 is a graph showing the time course of ventilatory depression in the ~~StellaTM~~ STELLA® computer model simulation of Figures 5A and 5B (ventilatory depression and sedation models enabled).

[0043] Figure 12 is a flow diagram which represents a computer simulation model for the administration of two opioids.

[0044] Figures 13A, 13B, and 13C, taken together, are a flow diagram which represents the ~~StellaTM~~ STELLA® computer model simulation of the pharmacokinetics of the administration of two opioids.

[0045] Figure 14 is a graph showing the output of ~~StellaTM~~ STELLA® computer model simulation of Figures 13A, 13B and 13C expressed as a time course of total quantity of opioid in the inhalation device and in the lung of the patient (ventilatory depression and sedation models enabled).

[0046] Figure 15 is a graph showing the time course of concentration of each opioid and of total opioid at the effect site in the ~~StellaTM~~ STELLA® computer model simulation of Figures 13A, 13B and 13C (ventilatory depression and sedation models enabled).

[0047] Figure 16 is a graph showing the time course of ventilatory depression during and after delivery of opioids in the ~~StellaTM~~ STELLA® computer model simulation of Figures 13A, 13B and 13C (ventilatory depression and sedation models enabled).

[0050] Figure 19 is a graph showing the time course of ventilatory depression in the ~~StellaTM~~ STELLA® computer model simulation of Figures 17A, 17B and 17C (ventilatory depression and sedation models enabled).

[0101] Figures 5A and 5B, taken together, are a flow diagram which represents the ~~StellaTM~~ STELLA® computer model simulation of the pharmacokinetics of the administration of a single opioid. Figure 5A shows the Device Model and the Pharmacokinetic Model aspects of the simulation, Figure 5B shows the Ventilatory Depression Model and the Sedation Model aspects of the simulation.

[0102] Figure 6 is a graph showing output of the ~~StellaTM~~ STELLA® computer model simulation of Figures 5A and 5B (ventilatory depression and sedation models disabled) expressed as a time course of quantity of opioid in the inhalation device, and quantity of opioid in the lung of the patient. The X axis shows time in minutes. The Y axis shows dose units of formulation, in mg. The amount of drug in the inhaler dropped steadily over the first 10 minutes of stimulation. The amount of drug in the lungs reflects the net processes of inhalation of drug into the lungs and absorbtion of drug from the lungs into the systemic circulation.

[0103] Figure 7 is a graph showing the time course of ventilatory depression in the ~~StellaTM~~ STELLA® computer model simulation of Figures 5A and 5B (ventilatory depression and sedation models disabled). Ventilatory depression (expressed as a fraction of baseline ventilation) was expressed over time of simulation (in minutes).

[0104] Figure 8 is a graph showing the time course of quantity of opioid in the inhalation device and in the lung of the patient, in the ~~StellaTM~~ STELLA® computer model simulation of Figures 5A and 5B (ventilatory depression model enabled, sedation model disabled). The X axis shows time in minutes. The Y axis shows dose units of formulation, in mg. Patient ventilation dropped to approximately 25% of baseline ventilation, such depression persisting for approximately 5-10 minutes.

[0105] Figure 9 is a graph showing the time course of ventilatory depression in the ~~StellaTM~~ STELLA® computer model simulation of Figures 5A and 5B (ventilatory depression model enabled, sedation model disabled). Ventilatory depression (expressed as a fraction of baseline ventilation) was expressed over time of simulation (in minutes). Change in ventilation caused by the self-limitation of opioid uptake offers considerable safety to the patient (compared to Figure 7).

[0106] Figure 10 is a graph showing the time course of quantity of opioid in the inhalation device and in the lung of the patient, in the ~~StellaTM~~ STELLA® computer

model simulation of Figures 5A and 5B (ventilatory depression and sedation models enabled). The X axis shows time in minutes. The Y axis shows dose units of formulation, in mg. Drug inhalation stopped completely at approximately 8 minutes, due to a sedation state being reached and self-limitation of drug intake.

[0107] Figure 11 is a graph showing the time course of ventilatory depression in the ~~StellaTM~~ STELLA® computer model simulation of Figures 5A and 5B (ventilatory depression and sedation models enabled). Ventilatory depression (expressed as a fraction of baseline ventilation) was expressed over time of simulation (in minutes). Change in ventilation caused by the self-limitation of opioid uptake from sedation offers considerable safety to the patient (compared to Figure 7 or 9).

[0109] Figures 13A, 13B and 13C, taken together, are a flow diagram which represents the ~~StellaTM~~ STELLA® computer model simulation of the pharmacokinetics of the administration of two opioids.

[0110] Figure 14 is a graph shwoing the output of ~~StellaTM~~ STELLA® computer model simulation of Figures 13A, 13B and 13C expressed as a time course of total quantity of opioid in the inhalation device and in the lung of the patient (ventilatory depression and sedation models enabled). Y axis shows fentanyl equivalents of formulation in the inhaler (1), of the rapid-onset opioid in the lung (2), and the sustained-effect opioid in the lung (3), expressed in ng/ml (fentanyl equivalents) of drug over time (in minutes). After approximately 12 minutes, the patient stopped inhaling more opioid, reflecting opioid-induced sedation.

[0111] Figure 15 is a graph showing the time course of concentration of each opioid and of total opioid at the effect site in the ~~StellaTM~~ STELLA® computer model simulation of Figures 13A, 13B and 13C (ventilatory depression and sedation models enabled). Amount of rapid-onset opioid (1), sustained-effect opioid (2) and the combination effect of both the rapid-onset opioid and the sustained-effect

opioid (3) at the site of effect were shown, in ng/ml of fentanyl equivalents, over time (in minutes).

[0112] Figure 16 is a graph showing the time course of ventilatory depression during and after delivery of opioids in the ~~StellaTM~~ STELLA® computer model simulation of Figures 14A, 14B and 14C (ventilatory depression and sedation models enabled). Ventilatory depression (expressed as a fraction of baseline ventilation) was expressed over time of simulation (in minutes). The combination fo the two opioids reaches a peak during the administration of the first opioid.

[0113] Figures 17A, 17B, and 17C, taken together, are a flow diagram which represents the ~~StellaTM~~ STELLA® computer model simulation of the pharmacokinetics of the administration of two opioids, where the two opioids being administered are alfentanil and morphine. Figures 17A and 17B show the Device Model and the Pharmacokinetic Model aspects of the simulation, while Figure 17C shows the Ventilatory Depression Model, the Sedation Model, and the Two Drug Model aspects of the simulation.